

Consumption of antibiotics in Greenland, 1964-70

III. Effect of coincidental administration of antibiotics on gonorrhoeal infections

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Cases of latent clinical infection and those with slight symptoms, often diagnosed only after the elapse of several months, are particularly exposed to the coincidental effects of antibiotics given to treat other conditions ('happenstance effect'). Since the course of infection in gonorrhoea is often very long, it is to be expected that a 'happenstance effect' will be evident in this disease, especially in areas where medical facilities are limited.

The present study surveys the effects which the antibiotic therapy most frequently used in non-venereal conditions (Olsen, 1973a) may have on unrecognized gonorrhoeal infections of varying duration. This evaluation has been used in an account of the changes in the resistance pattern of gonococci in Greenland (Olsen, 1973b).

Evaluation

It has been demonstrated that gonococci die after a few hours when exposed to adequate drug concentrations (Sabath and Kivlahan, 1961; Knudsen and Perdrup, 1963; Holmes, Johnson and Floyd, 1967). However, the choice of a suitable concentration and duration depends on the extent and duration of the infection, and particularly on the sensitivity of the infecting strain to the drug used. Wray (1965) found that there were almost twice as many failures as successes in men with gonococcal symptoms of more than 6 or 7 days' duration. Possibly because gonorrhoea in females is generally diagnosed later in the course of the infection than in males (Nicol, 1948; Nexmand, 1961; Ekström, 1972), the cure rate is often lower in women than in men. This is particularly true when the treatment used has a low rate of cure against infections caused by strains with reduced sensitivity (Krook and Juhlin, 1965). It is sometimes recommended, therefore, that a more intensive treatment should be used in females (Shapiro and Lentz, 1967; Lucas, 1971). It is difficult to determine whether the lower cure rate often found

in gonorrhoeal proctitis in females (Scott and Stone, 1966; Molin and Nyström, 1970) is due to the fact that these infections have lasted longer than in cases without proctitis, or to the failure of the drug used to reach curative levels in the rectum as well as in the urogenital tract.

The relationship between cure rate and the sensitivity of the strain *in vitro* has often been demonstrated. The studies of Gjessing and Ødegaard (1964), Schmidt (1962), and Borring (1965) are particularly instructive, since they give details of the cure rates at the various levels of sensitivity.

Gjessing and Ødegaard studied a series of 1,000 cases of uncomplicated gonorrhoea in males, all treated with 600,000 i.u. procaine penicillin. The heights of the columns in Fig. 1 show the cure rates obtained by these writers in 430 persons infected by strains with the sensitivities stated (the other 570 patients harboured strains sensitive to 0.015 or 0.03 i.u.). The Figure mostly includes those infections caused by strains with reduced sensitivities (MIC \geq 0.125 i.u. per ml.). It will be seen that the

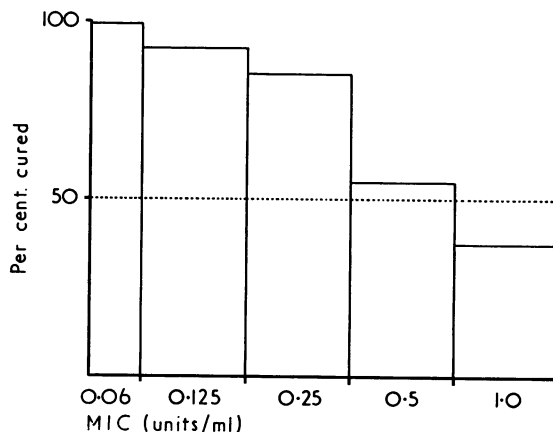


FIG. 1 Cure rate in gonorrhoeal infections related to *in vitro* sensitivities to penicillin (430 patients) (From Gjessing and Ødegaard, 1964)

50 per cent. cure rate with the treatment used was obtained in cases with strains sensitive to 0.5 to 1.0 i.u. per ml. penicillin. Schmidt (1962) used the same treatment in 108 males and females and found a 50 per cent. cure rate at about the same sensitivity level. Borring (1965), who used 300,000 i.u. procaine penicillin in 659 men and women also obtained a similar cure rate. Krook and Juhlin (1965) treated 519 females and 844 males with 900,000 i.u. procaine penicillin and obtained a 50 per cent. cure rate for females with strains sensitive to IC_{50} 0.1 to 2.5 i.u. per ml. and for males with strains sensitive to IC_{50} 0.5 to 2.5 i.u. per ml.

The work of Griffith and Peck (1958) indicates the serum levels produced by 600,000 i.u. procaine penicillin and the individual variations that occur. Fig. 2 shows the percentages of their subjects who showed various penicillin levels 6 and 12 hours after the injection. After 6 hours the level was 0.75 i.u. per ml. penicillin in almost 50 per cent., but this concentration was not found in any subject after 12 hours. The cure rate columns from Fig. 1 are shown also in Fig. 2 for comparison. The penicillin concentration found in 50 per cent. of the subjects after 6 hours corresponds to the sensitivity *in vitro* of the strains from cases in which 50 per cent. of the infections are cured. This agreement indicates that these infections had been cured in less than 6 hours, since the concentrations after 12 hours were clearly inadequate to produce the cure rate demonstrated clinically. Among the cases included in Gjessing and

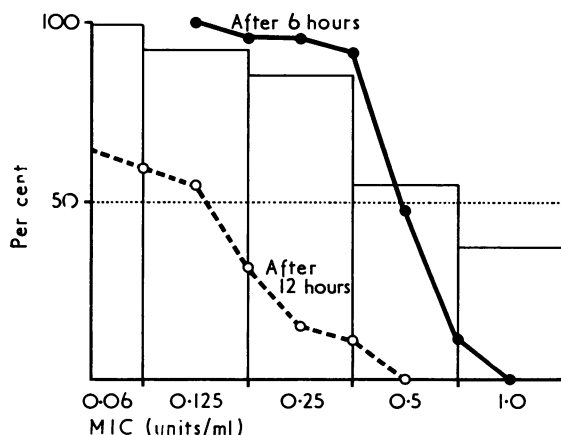


FIG. 2 Percentage subjects with penicillin concentrations in serum as shown—6 and 12 hours after injection of 600,000 i.u. procaine penicillin (25 males). From Griffith and Peck (1958) compared with Gjessing and Ødegaard's results from Fig. 1. (shown in background)

Ødegaard's series, there must have been some variation in the duration of the infection. It would seem (Fig. 2) that many more infections caused by strains with a sensitivity *in vitro* of ≥ 1.0 i.u. per ml. had been cured than would have been expected from the penicillin levels present after 6 hours. This is presumably because gonorrhoeal infections of limited duration can be cured by concentrations of penicillin that maintain a curative level in the blood stream for less than 6 hours. On the other hand, infections of longer duration may require the curative level to be maintained for more than 6 hours.

Antibiotic preparations which, by means of a higher initial concentration in the blood stream, achieve a curative level more rapidly at the site of the infection must be assumed to effect a cure in a shorter time. It is difficult to state the minimum duration of a curative level which is needed in gonorrhoeal infections until these parameters can be measured at the site of the infection, but comparisons mentioned above suggest this must be less than 6 hours in some cases. Eriksson (1971) found that 7 to 8 hours is probably the shortest effective duration when oral ampicillin is used to treat uncomplicated gonorrhoea of varying duration in both sexes. These minimum requirements may apply only to penicillin preparations; less information is available about other antibiotics, but tetracycline seems to act more slowly than penicillin (Holmes and others, 1967).

Griffith and Peck (1958) also measured the serum levels produced by oral penicillin treatment (400,000

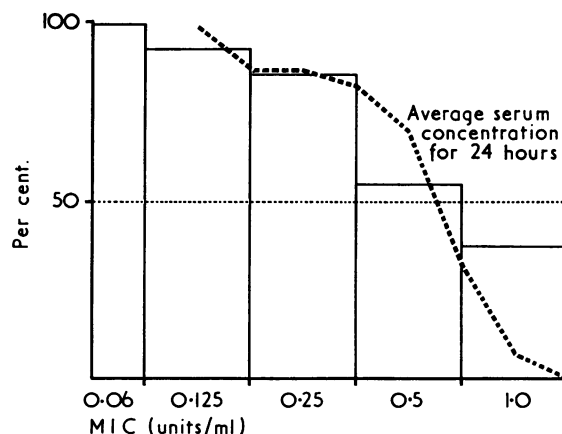


FIG. 3 Percentage subjects with penicillin concentrations in serum as shown (average of 24 hrs) during administration of V-penicillin 400,000 i.u. orally three times daily (25 males). From Griffith and Peck (1958) compared with Gjessing and Ødegaard's results from Fig. 1 (shown in background).

i.u. V-penicillin three times daily, as generally used in non-gonorrhoeal infections). The curve in Fig. 3 gives the percentage of persons who achieved different average serum concentrations for 24 hours. As would be expected, the concentrations achieved by oral treatment varied more than those obtained by parenteral treatment, but otherwise the level was about the same. Furthermore, Griffith and Peck found that, in the course of 14½ hours, there was an average level of ≥ 1.0 i.u. penicillin in the serum for 8 hours. Correspondingly, the serum concentration during a period of 16 hours was ≥ 0.75 i.u. for 11 hours, distributed into three periods of 5, 3, and 3 hours. It would be expected, therefore, that oral treatment with 400,000 i.u. V-penicillin three times a day would result in a cure rate corresponding to, or perhaps exceeding, that with 600,000 i.u. procaine penicillin. This was confirmed by King and Nicol (1964), who stated that good results were obtained with this dosage given for 3 days.

The serum levels obtained by oral tetracycline treatment are known from the studies of Doluisio and Dittert (1969) and of Holvey, Iles, and La Piana, (1970).

In both series increasing serum levels were observed from the first to the third day of treatment. Doluisio and Dittert (1969) found that the mean serum level after tetracycline phosphate 500 mg. twice daily averaged 1.0 µg./ml. after 1 day, 2.4 µg. after 2 days, and 3.2 µg. after 3 days. Holvey and others (1970) demonstrated peak levels of 3.4 to 4.0 µg./ml. from the 2nd to the 4th day after twice daily doses of 300 mg. demethylchlortetracycline. These levels could be expected to cure gonorrhoea where the sensitivity *in vitro* of the infecting strain was within the sensitive range (MIC up to 2.25 µg/ml). Among the strains less sensitive to tetracycline in Greenland (Olsen, 1973b) only four had an IC_{50} value of 1.60 µg./ml. (MIC 3.2 µg./ml.). Thus, coincidental treatment with 1 g. tetracycline phosphate daily for 3 days might be expected to cure most of the infections with less sensitive strains of gonococci in Greenland. In complicated or protracted infections, however, such treatment might prove subcurative and result in a further reduction of the sensitivity of the strain. The correlations between cure rates and sensitivity levels which were observed with penicillin are not yet established in relation to tetracycline.

The effect of antibiotic treatment on unrecognized gonorrhoeal infections must be expected to vary from country to country. This is due not only to differences in the drugs used and the usage pattern, but also to the varying resistance patterns of gonococcal strains and the different durations of gonorrhoeal infections. Further details concerning the

'happenstance effect' on the sensitivity pattern in an area in which medical facilities are limited will be given in a subsequent paper (Olsen, 1973b).

Summary

On the basis of antibiotic consumption in Greenland the coincidental effect of antibiotic treatment on unrecognized gonorrhoeal infections has been evaluated. The results depend on dosage and duration of treatment, on the sensitivity of the infecting strain to the drug used, and on the duration of the infection. The chances that this coincidental antibiotic effect may lead to an increased incidence of gonococcal strains with reduced sensitivity are therefore greatest where the resistance pattern is unfavourable, and where public health measures to check the spread of venereal diseases are limited.

The minimum duration of an adequate serum concentration of penicillin to effect cure is probably less than 6 hours in uncomplicated gonorrhoeal infections of short duration.

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